

University of Groningen

## **Efficacy and Safety of Canagliflozin in Patients with Type 2 Diabetes and Stage 3 Nephropathy**

Yamout, Hala; Perkovic, Vlado; Davies, Melanie; Woo, Vincent; de Zeeuw, Dick; Mayer, Cristiana; Vijapurkar, Ujjwala; Kline, Irina; Usiskin, Keith; Meininger, Gary

*Published in:*  
American Journal of Nephrology

*DOI:*  
[10.1159/000364909](https://doi.org/10.1159/000364909)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2014

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

Yamout, H., Perkovic, V., Davies, M., Woo, V., de Zeeuw, D., Mayer, C., Vijapurkar, U., Kline, I., Usiskin, K., Meininger, G., & Bakris, G. (2014). Efficacy and Safety of Canagliflozin in Patients with Type 2 Diabetes and Stage 3 Nephropathy. *American Journal of Nephrology*, 40(1), 64-74.  
<https://doi.org/10.1159/000364909>

### **Copyright**

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### **Take-down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

# Efficacy and Safety of Canagliflozin in Patients with Type 2 Diabetes and Stage 3 Nephropathy

Hala Yamout<sup>a</sup> Vlado Perkovic<sup>d</sup> Melanie Davies<sup>e</sup> Vincent Woo<sup>f</sup>  
Dick de Zeeuw<sup>g</sup> Cristiana Mayer<sup>b</sup> Ujjwala Vijapurkar<sup>c</sup> Irina Kline<sup>c</sup>  
Keith Usiskin<sup>c</sup> Gary Meininger<sup>c</sup> George Bakris<sup>a</sup>

<sup>a</sup>The University of Chicago Medicine, Chicago, Ill., Janssen Research & Development, LLC, <sup>b</sup>Titusville and  
<sup>c</sup>Raritan, N.J., USA; <sup>d</sup>George Institute for Global Health, Sydney, N.S.W., Australia; <sup>e</sup>University of Leicester,  
Diabetes Research Centre, Leicester, UK; <sup>f</sup>University of Manitoba, Winnipeg, Man., Canada; <sup>g</sup>University Medical  
Centre Groningen, Groningen, The Netherlands

## Key Words

Diabetes · Kidney · Nephropathy · Hypertension

## Abstract

**Background/Aims:** Some sodium glucose co-transporter 2 (SGLT2) inhibitors are approved for the treatment of patients with type 2 diabetes mellitus (T2DM) with an estimated glomerular filtration rate (eGFR) of  $\geq 45$  ml/min/1.73 m<sup>2</sup>. The efficacy and safety of canagliflozin, an approved SGLT2 inhibitor, was evaluated in patients with stage 3 chronic kidney disease (CKD; eGFR  $\geq 30$  to  $< 60$  ml/min/1.73 m<sup>2</sup>). **Methods:** This analysis used integrated data from four randomized, placebo-controlled, phase 3 studies that enrolled patients with T2DM and stage 3 CKD. Results are presented for the overall population as well as subgroups with stage 3a CKD (eGFR  $\geq 45$  and  $< 60$  ml/min/1.73 m<sup>2</sup>) and stage 3b CKD (eGFR  $\geq 30$  and  $< 45$  ml/min/1.73 m<sup>2</sup>). **Results:** Among all subjects studied with stage 3 CKD, placebo-subtracted reductions in HbA<sub>1c</sub> (−0.38 and −0.47%;  $p < 0.001$ ), body weight (−1.6 and −1.9%;  $p < 0.001$ ), and systolic blood pressure (−2.8 and −4.4 mm Hg;  $p < 0.01$ ) were seen with canagliflozin 100 and 300 mg, respectively. Decreases in HbA<sub>1c</sub>, body weight, and sys-

tolic blood pressure were examined in the stage 3a and 3b CKD subgroups, with greater decreases in HbA<sub>1c</sub> (−0.47% (−0.61, −0.32) and body weight in subjects in stage 3a CKD, −1.8% (−2.3, −1.2) with canagliflozin 100 mg. Initial declines in eGFR were seen early following treatment initiation with canagliflozin, but trended towards baseline over time. The most common adverse events with canagliflozin included genital mycotic infections and adverse events related to reduced intravascular volume likely secondary to osmotic diuresis. **Conclusion:** In subjects with T2DM and stage 3 CKD, canagliflozin reduced HbA<sub>1c</sub>, body weight, and blood pressure, and was generally well tolerated. © 2014 S. Karger AG, Basel

## Introduction

Chronic kidney disease (CKD) is a common complication in patients with type 2 diabetes mellitus (T2DM), with up to 30% of patients developing stage 3 or higher CKD (estimated glomerular filtration rate (eGFR)  $< 60$  ml/min/1.73 m<sup>2</sup>) within 15 years of diagnosis [1, 2]. Management of T2DM in patients with CKD represents a clin-

**Table 1.** Study design and subject description<sup>a</sup>

Study	Duration <sup>b</sup> , week	Inclusion criteria			Subjects contributing data to pooled analysis, n			
		age, years	HbA <sub>1c</sub> , %	eGFR ml/min/1.73 m <sup>2</sup>	PBO	CANA 100 mg	CANA 300 mg	total
Monotherapy	26	≥18 to ≤80	≥7.0, ≤10.0	≥50	10	10	12	32
CANagliflozin cardioVascular Assessment Study (CANVAS)	18	≥30	≥7.0, ≤10.5	≥30	252	208	246	706
Stage 3 CKD population	26	≥25	≥7.0, ≤10.5	≥30, <50	85	87	81	253
Older adults	26	≥55 to ≤80	≥7.0, ≤10.0	≥50	35	33	26	94
Overall total, n					382	338	365	1,085

PBO = Placebo; CANA = canagliflozin.

<sup>a</sup> Key exclusion criteria in common across the studies included repeated FPG >15.0 mmol/l (270 mg/dl) in general during the pre-treatment phase; history of T1DM, CV disease (including myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident) within 3 months prior to screening; or alanine aminotransferase (ALT) level >2.0 times the upper limit of normal (ULN) or total bilirubin >1.5 the ULN at screening. <sup>b</sup> Primary efficacy assessment time point.

ical challenge with limited treatment options, as most oral hypoglycemic agents have decreased efficacy and/or delayed clearance as well as more adverse events (AEs) among those with stage 3 or higher CKD [1, 3]. A novel class of oral agents, sodium glucose co-transporter 2 (SGLT2) inhibitors, provide physicians with an additional treatment option for patients with T2DM and stage 3 CKD.

The SGLT2 protein, expressed in the proximal tubules of the kidney, is responsible for about 90% of glucose reabsorption filtered through the glomerulus [4, 5]. Filtered glucose is almost fully reabsorbed until the transporters reach maximum glucose capacity; the plasma concentration at which this occurs is referred to as the renal threshold for glucose (RT<sub>G</sub>). Above this threshold, urinary glucose excretion increases in proportion to the plasma glucose concentration.

Canagliflozin is an orally active SGLT2 inhibitor developed for the treatment of patients with T2DM [6–13]. By inhibiting SGLT2, canagliflozin lowers RT<sub>G</sub>, resulting in increased glycosuria and osmotic diuresis, thus directly lowering plasma glucose concentrations in patients with elevated glucose levels [9, 14–16]. Increased urinary glucose excretion also results in weight loss due to loss of calories as well as reductions in blood pressure (BP) likely secondary to the osmotic diuresis. Moreover, while canagliflozin lowers RT<sub>G</sub> in patients with T2DM to approximately 4.4–5.5 mmol/l (80–100 mg/dl) [9, 14], it is above the usual threshold for hypoglycemia (≤3.9 mmol/l (70 mg/dl)), hence the risk of hypoglycemia with canagliflozin is relatively low. This paper provides analysis of

pooled data from *all* clinical trials that evaluated the safety and efficacy of canagliflozin in subjects with T2DM and stage 3 CKD.

## Materials and Methods

### Study Design, Patient Populations, and Treatments

Data were pooled from the cohorts enrolled in four randomized, placebo-controlled, phase 3 studies of subjects with T2DM with a baseline eGFR ≥30 and <60 ml/min/1.73 m<sup>2</sup> [17]. The studies included in this analysis are summarized in table 1 and include data from the canagliflozin monotherapy study [18], a study in subjects with T2DM and stage 3 CKD (with baseline eGFR ≥30 and <50 ml/min/1.73 m<sup>2</sup>) [13], a study in older subjects (aged 55–80) [6], and the ongoing CANagliflozin cardioVascular Assessment Study (CANVAS, interim data provided for regulatory filing) [19]. Due to the lack of a control group, data from subjects in the high glycemic subset (HbA<sub>1c</sub> >10.0 and ≤12.0%) of the monotherapy study were excluded from this analysis.

Across studies, eligible subjects included men and women with T2DM who had inadequate glycemic control at screening while on protocol-specified diabetes treatment regimens (diet and exercise for the monotherapy study and any approved agent for the other three studies). Patient inclusion and exclusion criteria and details of the individual study designs have previously been reported [6, 13, 18, 19].

In CANVAS and the study in older subjects, those meeting enrollment criteria entered a 2-week, placebo run-in period prior to randomization. In the monotherapy and stage 3 CKD studies, subjects who were not on protocol-specified background diabetes therapy or were on an anti-hyperglycemic agent (AHA) regimen not consistent with local prescribing information at screening, respectively, entered an AHA adjustment (or washout for the monotherapy study)/dose stable period prior to the placebo run-in period to meet study-specific criteria. In each study, subjects were

randomly assigned to receive once daily oral doses of canagliflozin 100 or 300 mg or placebo. In all studies, randomization was stratified to ensure adequate distribution of specific patient characteristics across treatment groups as previously reported [6, 13, 18, 19]. HbA<sub>1c</sub>, fasting plasma glucose (FPG), and postprandial glucose values were masked to study centers following randomization unless HbA<sub>1c</sub> and FPG values met pre-specified glycemic criteria for initiation of rescue therapy. Databases were locked at the primary assessment time point for each study, and studies were unblinded by the sponsor for regulatory filing; subjects and study center and local sponsor personnel remained blinded through completion of the respective double-blind treatment periods of each study.

Patients were to remain on stable diabetes treatment (diet/exercise and AHA regimen) throughout the double-blind treatment period. Those meeting pre-specified glycemic criteria were provided with rescue therapy (with metformin, monotherapy study, and uptitration of current AHAs or stepwise addition of other AHAs for CANVAS and studies in stage 3 CKD subjects and older subjects). In general, during the double-blind treatment period, glycemic rescue therapy was initiated if FPG >15.0 mmol/l (270 mg/dl) after day 1 to week 6, >13.3 mmol/l (240 mg/dl) after week 6 to week 12, and >11.1 mmol/l (200 mg/dl) after week 12 to week 26. For CANVAS, patient's glycemic goals and the need for adjustment in the AHA regimen were to be determined by the investigator after week 18. The mean duration of drug exposure in this trial was approximately 36 weeks, slightly longer in the canagliflozin groups compared to placebo.

All studies included in this analysis were conducted in accordance with ethical principles that comply with the Declaration of Helsinki and are consistent with Good Clinical Practice and applicable regulatory requirements. Institutional review boards at participating institutions approved study protocols and amendments. All subjects provided written informed consent prior to participation.

#### *Study Endpoints and Assessments*

Efficacy endpoints were evaluated at the primary assessment time point for each study (week 26 for the 3 studies and week 18 for CANVAS). Endpoints included change from baseline in HbA<sub>1c</sub> and the proportion of subjects achieving HbA<sub>1c</sub> <7.0%; change from baseline in FPG and systolic and diastolic BP; percent change from baseline in body weight (reported for data prior to rescue therapy).

Safety analyses included data up to week 26 for the monotherapy, stage 3 CKD, and older cohort studies, and a cutoff date of at least 18 weeks for CANVAS. Overall safety and tolerability were evaluated based on AE reports, safety laboratory tests, 12-lead electrocardiograms, vital sign measurements, self-monitored blood glucose, and physical examinations. Specific attention was given to AEs related to osmotic diuresis and reduced intravascular volume that may be associated with lower eGFR values. Pre-specified queries were constructed for each of these AEs using lists of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms consistent with the AE of interest; terms associated with each AE were grouped for analysis.

Documented hypoglycemia episodes, including biochemically documented episodes (concurrent fingerstick or plasma glucose ≤3.9 mmol/l (70 mg/dl) irrespective of symptoms) and severe hypoglycemia episodes (i.e. requiring the assistance of another individual or resulting in seizure or loss of consciousness), were also evaluated. Given the potential effect of background AHAs on the

risk of hypoglycemia, incidences of documented hypoglycemia are reported separately for subjects who were, or were not, on background AHA therapy associated with hypoglycemia (e.g. insulin, sulfonylureas).

Percent changes from baseline in fasting plasma lipids (i.e. triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), LDL-C/HDL-C ratio, and non-HDL-C) were evaluated. Laboratory safety assessments included blood chemistry (e.g. serum creatinine, eGFR), hematology, urinalysis, and urine albumin/creatinine ratio (ACR). Data for change in urine ACR are reported for the individual studies in subjects with stage 3 CKD and CANVAS. For evaluation of other clinical laboratory analyses, the proportion of subjects meeting predefined limits of change criteria was assessed based on any post-baseline measurement and on the last on-treatment measurement (defined as the last value within 2 days after the last dose of study medication).

#### *Statistical Methods*

Efficacy analyses were conducted using the modified intent-to-treat population, which consisted of all randomized subjects who received ≥1 dose of study drug, according to the randomized treatment assignment. The last observation carried forward (LOCF) approach was used to impute missing efficacy data. If subjects received rescue therapy, all post-rescue data were censored and the last post-baseline value prior to the initiation of rescue therapy was used for analyses. Continuous efficacy endpoints were assessed using an analysis of covariance (ANCOVA) model with treatment and study as factors and the respective baseline value as a covariate. Least squares (LS) mean differences and two-sided 95% confidence intervals (CIs) were estimated based on this model for the comparison of each canagliflozin group versus placebo with no multiplicity adjustment.

A sensitivity analysis of the change from baseline in HbA<sub>1c</sub> was also performed using the completers analysis set (i.e. subjects in the pooled population who completed the study through the primary assessment time point) using the same analysis approach. The categorical efficacy endpoint (i.e. proportion of subjects achieving HbA<sub>1c</sub> goals) was analyzed using a logistic regression model with treatment and study as factors and baseline HbA<sub>1c</sub> as covariate.

Safety analyses were performed in randomized subjects who received ≥1 dose of study drug. All AEs and lipids parameters are reported for regardless of rescue therapy; documented hypoglycemia episodes are reported for prior to rescue medication.

## **Results**

### *Baseline Characteristics*

The baseline demographic characteristics were similar among the treatment arms as listed in table 2. While the data represent a cross section of ethnic groups, there are lower percentages of some groups. Nevertheless, across all phase 3 studies in the canagliflozin program (n = 10,285 randomized subjects who had taken at least one dose of the study medication), the majority of the Black

**Table 2.** Baseline demographic and disease characteristics (total stage 3 CKD cohort)

Characteristic	PBO (n = 382)	CANA 100 mg (n = 338)	CANA 300 mg (n = 365)
Sex, n (%)			
Male	226 (59)	198 (59)	210 (58)
Female	156 (41)	140 (41)	155 (42)
Mean age $\pm$ SD, years	66.9 $\pm$ 7.6	67.3 $\pm$ 8.1	66.9 $\pm$ 7.4
Race, n (%) <sup>a</sup>			
White	309 (81)	260 (77)	280 (77)
Black or African-American <sup>b</sup>	9 (2)	9 (3)	13 (4)
Asian	50 (13)	43 (13)	48 (13)
Other <sup>c</sup>	14 (4)	26 (8)	24 (7)
Mean body mass index $\pm$ SD, kg/m <sup>2</sup>	33.0 $\pm$ 6.2	32.2 $\pm$ 6.1	32.3 $\pm$ 6.1
Mean triglycerides $\pm$ SD, mmol/l	2.1 $\pm$ 1.3	2.0 $\pm$ 1.1	2.0 $\pm$ 1.0
Mean LDL-C $\pm$ SD, mmol/l	2.4 $\pm$ 0.9	2.3 $\pm$ 0.9	2.3 $\pm$ 1.0
Mean eGFR $\pm$ SD, ml/min/1.73 m <sup>2</sup>	48.8 $\pm$ 8.0	48.0 $\pm$ 8.5	47.8 $\pm$ 8.2
Mean ACR $\pm$ SD, g/mol	23.3 $\pm$ 63.0	20.1 $\pm$ 51.8	26.4 $\pm$ 87.1
Mean potassium $\pm$ SD, mEq/l	4.6 $\pm$ 0.5	4.5 $\pm$ 0.5	4.6 $\pm$ 0.6
Mean duration of T2DM $\pm$ SD, years	15.0 $\pm$ 9.0	15.0 $\pm$ 7.9	15.4 $\pm$ 8.3
Daily cigarette smoker at study entry, n (%)	45 (11.8)	32 (9.5)	33 (9.0)
Patients on AHA at baseline, n (%)	365 (95.5)	321 (95.0)	346 (94.8)
Biguanide <sup>d</sup>	147 (38.5)	111 (32.8)	107 (29.3)
Sulfonylurea <sup>d</sup>	160 (41.9)	128 (37.9)	141 (38.6)
Insulin <sup>d</sup>	219 (57.3)	208 (61.5)	221 (60.5)
Patients on antihypertensive medication at baseline, n (%) <sup>e</sup>	345 (90.3)	307 (90.8)	326 (89.3)
ACE inhibitor	191 (50.0)	146 (43.2)	164 (44.9)
ARB	131 (34.3)	120 (35.5)	121 (33.2)
ACE inhibitor + ARB	18 (4.7)	20 (5.9)	17 (4.7)
ACE inhibitor + diuretic	8 (2.1)	18 (5.3)	12 (3.3)
ARB + diuretic	14 (3.7)	16 (4.7)	20 (5.5)

PBO = Placebo; CANA = canagliflozin.

<sup>a</sup> Percentages may not total 100% due to rounding. <sup>b</sup> Black/African-American patients represent 10% (30/299) of patients with stage 3 CKD from the USA. <sup>c</sup> Includes American-Indian or Alaska Native, Native Hawaiian or other Pacific Islanders, multiple, other, not reported, and unknown. <sup>d</sup> Alone or in combination with other AHAs. <sup>e</sup> ACE inhibitor or ARB or diuretic.

or African-American subjects were recruited from the USA and represent approximately 14% (359/2634) of the subjects randomized from the USA, consistent with the proportion having T2DM in the USA in this population. Note that the studies discussed in this analysis did not mandate a pre-specified breakdown of racial and ethnic representation, however the data are consistent with the proportion of African-Americans having T2DM in the USA.

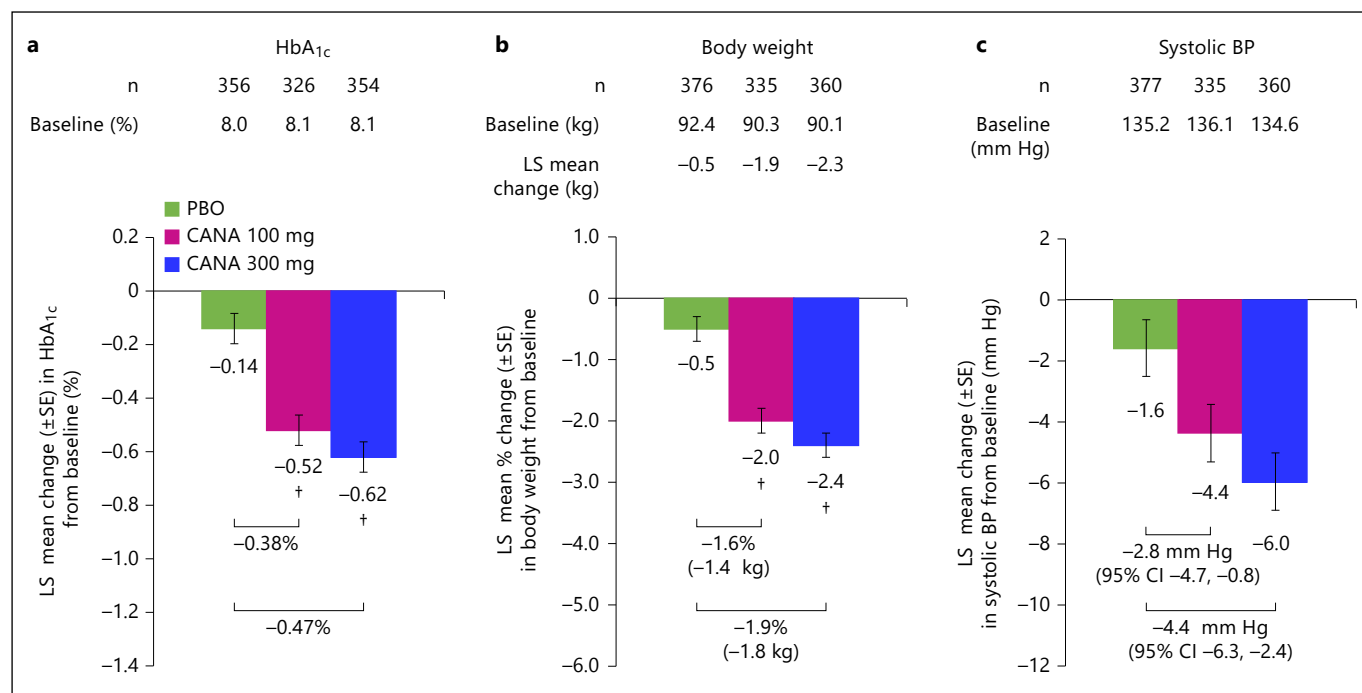
Evaluation of subgroups based on eGFR showed that those with stage 3b CKD were older and had a longer mean duration of T2DM as compared to those with stage 3a CKD, although HbA<sub>1c</sub> was similar in both subgroups (online suppl. table 1; for all online suppl. material, see [www.karger.com/doi/10.1159/000364909](http://www.karger.com/doi/10.1159/000364909)). Those with stage 3a CKD had a mean  $\pm$  SD baseline eGFR of 53.3  $\pm$

4.2 ml/min/1.73 m<sup>2</sup> compared to those with stage 3b CKD who had a mean GFR of 38.2  $\pm$  4.1 ml/min/1.73 m<sup>2</sup>. Overall, 90.1% of subjects were receiving either an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or a diuretic; 88.1% of those with stage 3a CKD were on these medications, as were 94.2% of those with stage 3b CKD.

### Efficacy

#### Total Cohort of Subjects with Stage 3 CKD

In the overall cohort of subjects with stage 3 CKD, significant reductions in HbA<sub>1c</sub> were seen with canagliflozin 100 and 300 mg relative to placebo (LS mean differences (95% CI) of -0.38% (-0.50, -0.26) and -0.47% (-0.60, -0.35), respectively;  $p < 0.001$ ; fig. 1a). Results of the sensitivity analysis using the completers analysis set showed



**Fig. 1.** Changes in (a) HbA<sub>1c</sub>, (b) body weight, and (c) systolic BP for the overall stage 3 CKD population. SE = Standard error; PBO = placebo; CANA = canagliflozin. Note: Statistical comparison for changes in systolic BP with CANA 100 and 300 mg vs. PBO not performed (not pre-specified). <sup>†</sup>  $p < 0.001$  vs. PBO.

similar placebo-subtracted LS mean changes (95% CI) of -0.31% (-0.44, -0.19) and -0.41% (-0.53, -0.28) with canagliflozin 100 and 300 mg, respectively;  $p < 0.001$ . The proportion of subjects achieving HbA<sub>1c</sub> <7.0% was higher with canagliflozin 100 and 300 mg compared with placebo (24.5, 31.9, and 17.4%, respectively;  $p < 0.001$  for canagliflozin 300 mg vs. placebo). Canagliflozin 100 and 300 mg were also associated with reductions in FPG relative to placebo (LS mean differences (95% CI) of -1.1 mmol/l (-1.4, -0.7) and -1.2 mmol/l (-1.6, -0.9), respectively; -18.8 mg/dl (-25.4, -12.4) and -22.0 mg/dl (-28.4, -15.6), respectively;  $p < 0.001$ ).

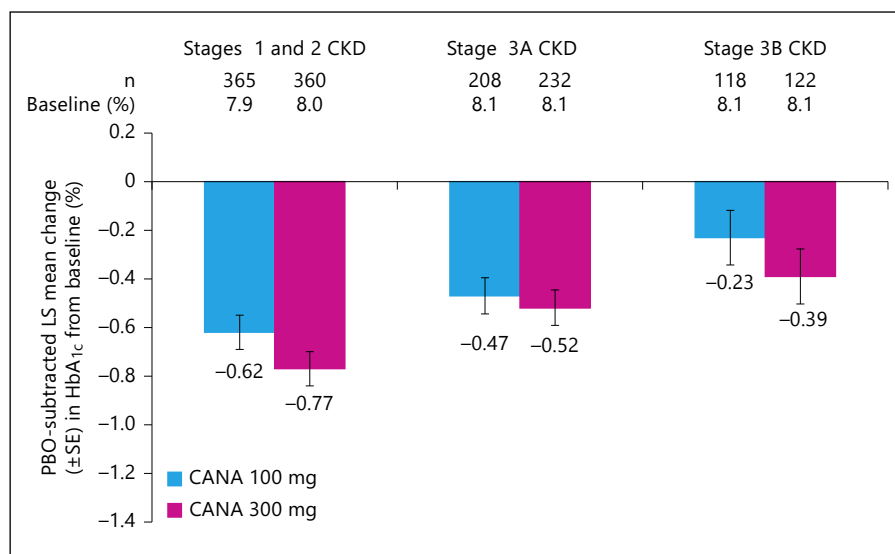
There is no formal comparison of the glucose-lowering effect of canagliflozin between those with an eGFR >60 ml/min/1.73 m<sup>2</sup> and those with stage 3 CKD. Glycemic efficacy, however, was demonstrated in subjects with CKD stage 3 renal disease (fig. 2), albeit with a lesser extent of glucose lowering than seen in subjects with stages 1 or 2 CKD. Nonetheless, canagliflozin got more subjects with stage 3 CKD to the glycemic goal (HbA<sub>1c</sub> <7%). The changes in HbA<sub>1c</sub> are not confounded since these patients did not have anemia given baseline hemoglobin values 13.45, 13.44 and 13.54 g/dl in the placebo, canagliflozin 100- and 300-mg groups, respectively.

Body weight was significantly reduced in the overall population of subjects with stage 3 CKD with canagliflozin 100 and 300 mg compared with placebo (LS mean (placebo-subtracted) differences (95% CI) of -1.6% (-2.0, -1.1) and -1.9% (-2.3, -1.5), respectively; -1.4 kg (-1.8, -1.0) and -1.8 kg (-2.1, -1.4), respectively;  $p < 0.001$ ; fig. 1b). Canagliflozin 100 and 300 mg were also associated with reductions in systolic BP relative to placebo (LS mean differences (95% CI) of -2.8 mm Hg (-4.7, -0.8) and -4.4 mm Hg (-6.3, -2.4), respectively; fig. 1c). Generally, only minimal changes in fasting plasma lipids were observed with canagliflozin 100 and 300 mg compared with placebo (online suppl. table 2).

#### Stage 3a CKD Subgroup

In the subgroup of subjects with stage 3a CKD, placebo-subtracted LS mean reductions (95% CI) in HbA<sub>1c</sub> were -0.47% (-0.61, -0.32) and -0.52% (-0.67, -0.38) with canagliflozin 100 and 300 mg, respectively (online suppl. table 3). The proportion of subjects achieving HbA<sub>1c</sub> <7.0% was 26.0, 32.8 and 19.4% with canagliflozin 100 and 300 mg and placebo, respectively. Placebo-subtracted LS mean reductions (95% CI) in FPG were also seen with canagliflozin 100 mg (-1.2 mmol/l (-1.6, -0.8);





**Fig. 2.** Comparison of placebo-subtracted effect of canagliflozin in people with stages 1 and 2 CKD versus stage 3 CKD. Data taken from online supplementary table 3 and metformin add-on study in normal subjects.

–21.8 mg/dl (–29.4, –14.2)) and 300 mg (–1.3 mmol/l (–1.7, –0.9); –23.0 mg/dl (–30.4, –15.6)).

Placebo-subtracted LS mean percent reductions (95% CI) in body weight were –1.8% (–2.3, –1.2) and –2.0% (–2.5, –1.5) with canagliflozin 100 and 300 mg, respectively (online suppl. table 3). Placebo-subtracted LS mean reductions (95% CI) in systolic BP of –1.8 mm Hg (–4.1, 0.5) and –4.3 mm Hg (–6.5, –2.0) with canagliflozin 100 and 300 mg, respectively, were seen in stage 3a CKD subjects (online suppl. table 3). Changes in fasting plasma lipids were generally similar in the stage 3a CKD subgroup compared with the overall population, with the exception of larger percent increases in LDL-C with canagliflozin versus placebo in this subgroup (online suppl. table 4).

#### Stage 3b CKD Subgroup

Placebo-subtracted LS mean reductions (95% CI) in HbA<sub>1c</sub> in the stage 3b CKD subgroup were –0.23% (–0.45, –0.01) and –0.39% (–0.61, –0.17) with canagliflozin 100 and 300 mg, respectively. With canagliflozin 100 and 300 mg and placebo, 22.0, 30.3 and 13.0% of subjects, respectively, achieved HbA<sub>1c</sub> <7.0%. Reductions in FPG were observed with canagliflozin 100 and 300 mg relative to placebo (LS mean differences (95% CI) of –0.7 mmol/l (–1.4, –0.02) and –1.1 mmol/l (–1.8, –0.4), respectively; –12.8 mg/dl (–25.2, –0.4) and –19.6 mg/dl (–32.1, –7.2), respectively).

Canagliflozin 100 and 300 mg were associated with reductions in body weight compared with placebo (placebo-subtracted LS mean percent reductions (95% CI) of –1.2% (–1.9, –0.5) and –1.8% (–2.5, –1.1), respectively;

online suppl. table 3). Placebo-subtracted LS mean reductions (95% CI) in systolic BP with canagliflozin 100 and 300 mg were similar in the stage 3b CKD subgroup (–4.8 mm Hg (–8.5, –1.2) and –4.9 mm Hg (–8.5, –1.2), respectively; online suppl. table 3) compared with the overall population. Compared to placebo, both doses of canagliflozin showed reductions in LDL-C, LDL-C/HDL-C ratio, and non-HDL-C and increases in HDL-C. A relative decrease in triglycerides was seen with canagliflozin 100 mg and an increase with canagliflozin 300 mg (online suppl. table 4).

#### Safety and Tolerability

There was a higher incidence of AEs in those taking canagliflozin compared with placebo in the overall population as well as the stage 3a and 3b CKD subgroups (table 3 and online suppl. table 5), however there were more serious AEs in the placebo group. In general, more subjects receiving canagliflozin 300 mg had to discontinue the drug due to AEs compared to those receiving canagliflozin 100 mg and placebo. In subjects with stage 3b CKD, however, AE-related discontinuation rates were higher in both canagliflozin dose groups compared with placebo (online suppl. table 5). The higher rate of discontinuation in those receiving 300 mg was primarily related to AEs associated with reduced intravascular volume such as postural dizziness and hypotension as well as early and reversible reductions in eGFR.

In the overall CKD cohort, the incidence of AEs related to osmotic diuresis, including increased urine output and/or frequency, and thirst, was similar across groups, and

**Table 3.** Summary of overall safety and selected AEs (total stage 3 CKD cohort)<sup>a</sup>

Patients, n (%)	PBO (n = 382)	CANA 100 mg (n = 338)	CANA 300 mg (n = 365)
Any AE	269 (70.4)	250 (74.0)	275 (75.3)
AEs leading to discontinuation	22 (5.8)	19 (5.6)	28 (7.7)
AEs related to study drug <sup>b</sup>	82 (21.5)	96 (28.4)	119 (32.6)
Serious AEs	75 (19.6)	45 (13.3)	54 (14.8)
Deaths	6 (1.6)	3 (0.9)	5 (1.4)
Canagliflozin mechanism-related AE			
Osmotic diuresis-related AEs <sup>c</sup>	14 (3.7)	14 (4.1)	14 (3.8)
Serious AEs	0	0	0
Events leading to discontinuation	0	0	0
Volume-related AEs <sup>d</sup>	10 (2.6)	17 (5.0)	31 (8.5)
Serious AEs	5 (1.3)	1 (0.3)	3 (0.8)
Events leading to discontinuation	0	1 (0.3)	2 (0.5)
Renal-related AEs <sup>e</sup>	14 (3.7)	30 (8.9)	34 (9.3)
Serious AEs	5 (1.3)	4 (1.2)	5 (1.4)
Events leading to discontinuation	4 (1.0)	4 (1.2)	6 (1.6)
Urinary tract infection	23 (6.0)	21 (6.2)	27 (7.4)
Serious AEs	3 (0.8)	1 (0.3)	0
Events leading to discontinuation	2 (0.5)	1 (0.3)	0
Female genital mycotic infection <sup>f,g</sup>	3 (1.9)	15 (10.7)	16 (10.3)
Serious AEs	0	0	0
Events leading to discontinuation	0	1 (0.7)	1 (0.6)
Male genital mycotic infection <sup>g,h</sup>	3 (1.3)	5 (2.5)	15 (7.1)
Serious AEs	0	0	0
Events leading to discontinuation	0	0	2 (1.0)
AEs reported in ≥2% of patients and ≥0.5% higher with any CANA group vs. PBO			
Constipation	7 (1.8)	8 (2.4)	10 (2.7)
Diarrhea	21 (5.5)	9 (2.7)	24 (6.6)
Chest pain	7 (1.8)	5 (1.5)	9 (2.5)
Fatigue	8 (2.1)	9 (2.7)	8 (2.2)
Gastroenteritis	5 (1.3)	7 (2.1)	2 (0.5)
Blood urea increased	6 (1.6)	7 (2.1)	12 (3.3)
Back pain	12 (3.1)	11 (3.3)	13 (3.6)
Osteoarthritis	6 (1.6)	7 (2.1)	4 (1.1)
Pain in extremity	6 (1.6)	11 (3.3)	8 (2.2)
Headache	10 (2.6)	16 (4.7)	9 (2.5)
Dyspnea	6 (1.6)	8 (2.4)	2 (0.5)
Rash	5 (1.3)	4 (1.2)	8 (2.2)
Skin ulcer	2 (0.5)	9 (2.7)	5 (1.4)

PBO = Placebo; CANA = canagliflozin.

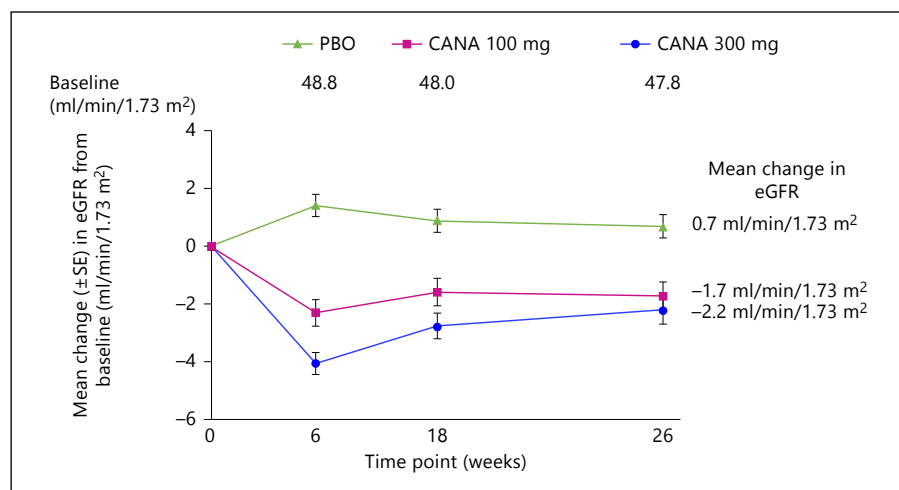
<sup>a</sup> All AEs are reported for regardless of rescue medication. <sup>b</sup> Possibly, probably, or very likely related to study drug, as assessed by investigators. <sup>c</sup> Including micturition urgency, nocturia, pollakiuria, polyuria, urine output increased, dry mouth, and thirst. <sup>d</sup> Including dehydration, dizziness postural, hypotension, orthostatic hypotension, presyncope, and syncope. <sup>e</sup> Including blood creatinine increased, GFR decreased, oliguria, renal failure, renal failure acute, and renal impairment. <sup>f</sup> PBO, n = 156; CANA 100 mg, n = 140; CANA 300 mg, n = 155. <sup>g</sup> AE included in the grouped terms are not reported. <sup>h</sup> PBO, n = 226; CANA 100 mg, n = 198; CANA 300 mg, n = 210.

did not lead to study discontinuation. Reduced intravascular volume-related AEs, such as postural dizziness and orthostatic hypotension, were seen more frequently in the canagliflozin 100- and 300-mg groups compared with the placebo group. The incidence of urinary tract infections (UTIs) was slightly higher with canagliflozin 300 mg ver-

sus canagliflozin 100 mg and placebo, without an observed increase in rate of upper UTIs across groups. An increased incidence of genital mycotic infections in males and females was seen with canagliflozin versus placebo; these AEs generally did not lead to study discontinuation. No notable differences in the incidence of these specific



**Fig. 3.** Changes in eGFR among all stage 3 CKD participants. PBO = Placebo; CANA = canagliflozin; SE = standard error. Note: Data are reported regardless of rescue medication and up to within 2 days after the last dose of study drug.



AEs from placebo were seen in subjects with stage 3a CKD. In subjects with stage 3b CKD, however, there was a higher incidence of side effects related to volume depletion and UTIs in the canagliflozin 300-mg group (online suppl. table 5) compared with the overall cohort.

#### Hypoglycemia

The incidence and severity of hypoglycemia varied depending on background AHA therapy. Of the 88.2% of subjects in the overall population treated with insulin and/or a sulfonylurea, 41.9 and 43.8% in the canagliflozin 100- and 300-mg groups, respectively, experienced hypoglycemia episodes documented by decreases in plasma glucose to  $\leq 3.9$  mmol/l (70 mg/dl), as compared to 29.2% in the placebo group. There were 20 subjects who experienced severe hypoglycemia episodes (4 (1.2%) with placebo, 9 (3%) with canagliflozin 100 mg, and 7 (2.2%) with canagliflozin 300 mg). Of those who were not on insulin and/or a sulfonylurea, the incidence of hypoglycemia was low, with documented (based on plasma glucose) hypoglycemia reported in 1 patient (2%) in the placebo group, 3 (8.1%) in the canagliflozin 100-mg group, and 1 (2.4%) in the canagliflozin 300-mg group. There were no severe hypoglycemic episodes among subjects not taking insulin and/or a sulfonylurea.

#### Assessment of Kidney Function

Changes in eGFR with canagliflozin in the overall cohort demonstrated a small initial decline followed by return towards trend to baseline (fig. 3) (the changes in eGFR for stages 3a and 3b CKD are provided in online suppl. fig. 1). These changes suggest an early hemodynamic effect, seen within days of treatment followed by

attenuation over time. When endpoint analyses were performed in the overall population, mean eGFR decreased by  $-1.7$  and  $-2.2$  ml/min/1.73 m<sup>2</sup> in those treated with canagliflozin 100 and 300 mg, respectively, while it rose by  $0.7$  ml/min/1.73 m<sup>2</sup> in the placebo group. Similar mean changes were seen with canagliflozin 100 and 300 mg compared with placebo at week 26 in the stage 3a CKD subgroup ( $-1.4$ ,  $-2.3$ , and  $1.0$  ml/min/1.73 m<sup>2</sup>, respectively) and the stage 3b CKD subgroup ( $-2.4$ ,  $-2.1$ , and  $0.01$  ml/min/1.73 m<sup>2</sup>, respectively).

In the dedicated study of subjects with stage 3 CKD (table 1), 29 subjects with macroalbuminuria at baseline ( $>300$   $\mu$ g/mg; 14 in the placebo group, 7 in the canagliflozin 100-mg group and 8 in the canagliflozin 300-mg group), showed mean percent reductions (SD) in albuminuria of  $-19.6$  (47.3),  $-53.1$  (17.4), and  $-44.7$  (36.0)%, respectively.

The incidence of kidney-associated AEs (e.g. increased serum creatinine, decreased eGFR, renal failure, and kidney function impairment) were higher with canagliflozin than with placebo (table 3) and generally higher in those with stage 3b CKD (online suppl. table 5). In the overall population, the most common specific terms for renal AEs in the pooled canagliflozin group were blood creatinine increased (5.3%), renal impairment (2.4%), and GFR decreased (1.3%).

#### Changes in Serum Potassium

No significant changes in mean serum potassium were seen with canagliflozin 100 and 300 mg compared with placebo in the overall population ( $-0.01$ ,  $0.07$ , and  $0.02$  mEq/l (mmol/l), respectively), the stage 3a CKD subgroup ( $0.05$ ,  $0.10$ , and  $0$  mEq/l (mmol/l), respectively), or

the stage 3b CKD subgroup ( $-0.12$ ,  $0.02$ , and  $0.07$  mEq/l (mmol/l), respectively). Based on any post-baseline value, the proportion of subjects experiencing increased serum potassium above the upper limit of normal and  $>15\%$  increase from baseline with placebo, canagliflozin 100 and 300 mg was 7.9, 7.2, and 12.0%, respectively, in the overall population; 5.5, 5.2, and 9.1%, respectively, in the stage 3a CKD subgroup, and 13.5, 10.9, and 17.4%, respectively, in the stage 3b CKD subgroup. When assessed based on the last post-baseline value, fewer subjects had an increase in serum potassium above the upper limit of normal and  $>15\%$  increase from baseline in the overall population (3.0, 1.8 and 3.1%, in the placebo, canagliflozin 100- and 300-mg groups, respectively), the stage 3a CKD subgroup (3.1, 1.9, and 1.7%, respectively), and the stage 3b CKD subgroup (2.7, 1.7, and 5.8%, respectively). Few subjects had any post-baseline potassium elevations that were  $\geq 6.5$  mEq/l with canagliflozin 100 and 300 mg and placebo in the overall population (1.1, 0.9, and 2.3%, respectively), the stage 3a CKD subgroup (0.8, 0, and 1.3%, respectively), and the stage 3b CKD subgroup (1.8, 2.5, and 4.1%, respectively).

### Phosphate

Using post-baseline data the proportion of subjects with increasing serum phosphate levels above the upper limit of normal and  $>25\%$  increase from baseline with placebo, canagliflozin 100 and 300 mg was 0.3, 2.7, and 5.1%, respectively. When assessed based on the last post-baseline value, fewer subjects had an increase in serum phosphate above the upper limit of normal and  $>25\%$  increase from baseline in the overall population (0, 0.6 and 1.4%, in the placebo, canagliflozin 100- and 300-mg groups, respectively).

Serious AEs related to elevated potassium were reported in 3 subjects (1 with canagliflozin 100 mg and 2 with canagliflozin 300 mg), all receiving multiple antihypertensive agents affecting potassium homeostasis. All three serious events coincided with an acute event, e.g. renal failure, and two led to study discontinuation, both with canagliflozin 300 mg.

## Discussion

We evaluated the effects of canagliflozin in a pooled analysis of four randomized, placebo-controlled trials involving T2DM subjects with stage 3 CKD. Canagliflozin improved glycemic control in subjects with stage 3 CKD, with a greater effect observed in subjects with stage 3a CKD. Mean reductions in stage 3b CKD were smaller,

however, still more subjects achieved an HbA<sub>1c</sub> goal of  $<7.0\%$  compared to placebo.

Canagliflozin 100 mg once daily is recommended for use in management of T2DM in subjects with an eGFR of 45 to  $<60$  ml/min/1.73 m<sup>2</sup> [20]. In the USA, canagliflozin 100 mg can be initiated in subjects with an eGFR  $\geq 45$  ml/min/1.73 m<sup>2</sup>. In Europe, patients must have baseline eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> to initiate canagliflozin therapy; however, patients whose eGFR falls persistently to  $<60$  ml/min/1.73 m<sup>2</sup> can continue treatment with canagliflozin 100 mg unless eGFR falls below 45 ml/min/1.73 m<sup>2</sup>.

The mechanism of canagliflozin action results in an osmotic diuresis and caloric loss, which contributes to both weight loss and BP reduction. BP control is a major concern in patients with stage 3 CKD and hypertension is one of the most important risk factors that influences CKD progression, as well as the risk of cardiovascular events. Canagliflozin reduces BP in those with stage 3 CKD, further enhancing systolic BP reduction by an additional 3–7 mm Hg on top of renin-angiotensin system blocking therapy and diuretics [21].

Reduced intravascular volume and decreased eGFR were also observed in patients with stage 3 CKD, mostly within the first months of treatment and, in a small subgroup, resulted in drug discontinuation or other antihypertensive drug modification. A dose-dependent increase in AEs related to reduced intravascular volume was seen with canagliflozin in the CKD cohort. Initial declines in eGFR of 10–15% trended toward baseline after about 6 weeks. These changes are likely due to hemodynamic effects on the kidney, and do not suggest progressive renal injury in subjects with stage 3 CKD. By blocking SGLT2-dependent glucose reabsorption, SGLT2 inhibitors such as canagliflozin are expected to increase the sodium concentration in the proximal convoluted tubule, thereby activating tubuloglomerular feedback, leading to a decrease in hyperfiltration in preclinical models and clinical studies of diabetes [22, 23]. Small increases in LDL-C have been associated with canagliflozin treatment [6–8, 10–13, 18]. The mechanism for this is not completely understood. In the current analysis, percent increases in LDL-C were seen with canagliflozin 100 and 300 mg compared with placebo in the overall population and the stage 3a CKD subgroup, but decreases in LDL-C were seen in the stage 3b CKD subgroup. This is likely related to the greater increase in LDL-C in the placebo group in the stage 3b CKD subgroup.

An increase in UTIs and genital mycotic infections has been previously reported [24]. In the overall population, the incidence of UTIs was slightly higher with canagliflozin 300 mg versus canagliflozin 100 mg and placebo;

there was no difference across groups in upper UTIs. Incidences of genital mycotic infections in males and females were higher with both doses of canagliflozin compared with placebo. However, these AEs were mild to moderate in intensity, generally did not lead to study drug discontinuation or interruption, and were treated by either a healthcare professional or by the patient with either topical or oral antifungal agents. The incidence of fracture AEs was not assessed in the current analysis, but a previous study in subjects with eGFR  $\geq 30$  and  $< 50$  ml/min/1.73 m<sup>2</sup> showed a low incidence of fractures with canagliflozin 100 and 300 mg and placebo, with no imbalance between groups [13].

The incidence of serum potassium elevation was increased with canagliflozin 300 mg compared with placebo with no incremental changes observed with canagliflozin 100 mg, the dosage indicated in patients with stage 3a CKD in the USA. In general, elevations in potassium were transient and did not require specific treatment. Significant elevations in serum potassium were uncommon and more frequently seen in patients with stage 3b CKD who received either the 300-mg dose, had elevated serum potassium concentrations prior to treatment, and/or were on multiple medications that reduce potassium excretion. However, there was no notable increase in incidence of hyperkalemia, i.e. serum potassium  $\geq 6.5$  mEq/l with canagliflozin, even in the stage 3b CKD subgroup. Changes in potassium with canagliflozin did not appear related to changes in eGFR, blood urea nitrogen, or hemoglobin or to reduced intravascular volume. Of note, there were no other major electrolyte abnormalities associated with use of this drug.

There are limitations to the analyses presented in that they represent pooled data and are drawn from cohorts

that do not fully represent the cross section of ethnic groups with diabetic kidney disease, i.e. American-Indians, Asian-Pacific Islanders and relatively low numbers of African-Americans and Hispanics. Nevertheless, the data are consistent in both safety and efficacy and there is no mechanistic reason to think the response would be different in these underrepresented groups.

In summary, the oral treatment options for T2DM patients with stage 3a CKD are limited to reduced doses of either metformin, peroxisome proliferator-activated receptor- $\gamma$  agents, or dipeptidyl peptidase 4 inhibitors [25]. Insulin and sulfonylureas may lead to weight gain, edema, or hypoglycemia. Certain SGLT2 inhibitors, namely canagliflozin, provide a new treatment option to help achieve glycemic control in T2DM patients with stage 3a CKD. The medication is well tolerated overall with the most common AEs relating to genital mycotic infections and enhanced risk of intravascular volume reduction, the latter also occurring in patients aged  $\geq 75$  years, and on loop diuretics. The effects of canagliflozin on CKD progression in man is currently being studied in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE) [26]. The results will provide the answer as to whether SGLT2 inhibition slows nephropathy progression.

## Disclosure Statement

The primary (H.Y.) and senior authors (G.B.) as well as (V.P., M.D., V.W. and D.D.Z.) received no compensation for this work. G.B., V.P., D.D.Z., M.D. and V.W. are consultants for Janssen Pharma. The remaining authors are employees of Janssen Pharma.

## References

- 1 Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR: Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;35:1364–1379.
- 2 Koro CE, Lee BH, Bowlin SJ: Antidiabetic medication use and prevalence of chronic kidney disease among patients with type 2 diabetes mellitus in the United States. *Clin Ther* 2009;31:2608–2617.
- 3 Reilly JB, Berns JS: Selection and dosing of medications for management of diabetes in patients with advanced kidney disease. *Semin Dial* 2010;23:163–168.
- 4 Bailey CJ: Renal glucose reabsorption inhibitors to treat diabetes. *Trends Pharmacol Sci* 2011;32:63–71.
- 5 Nair S, Wilding JP: Sodium glucose co-transporter 2 inhibitors as a new treatment for diabetes mellitus. *J Clin Endocrinol Metab* 2010;95:34–42.
- 6 Bode B, Stenlof K, Sullivan D, Fung A, Usiskin K: Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract* (1995) 2013;41:72–84.
- 7 Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, Balis DA, Canovatchel W, Meininger G: Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52-week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 2013;382:941–950.
- 8 Lavalley-Gonzalez FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W, Meininger G: Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 2013;56:2582–2592.
- 9 Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, Capuano G, Canovatchel W: Dose-ranging effects of canagliflozin, a sodium-glucose co-transporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care* 2012;35:1232–1238.

- 10 Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W, Meininger G: Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care* 2013;36:2508–2515.
- 11 Stenlof K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G: Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab* 2013;15:372–382.
- 12 Wilding JP, Charpentier G, Hollander P, Gonzalez-Galvez G, Mathieu C, Vercruysse F, Usiskin K, Law G, Black S, Canovatchel W, Meininger G: Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. *Int J Clin Pract* 2013;67:1267–1282.
- 13 Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, Figueroa K, Wajs E, Usiskin K, Meininger G: Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 2013;15:463–473.
- 14 Devineni D, Morrow L, Hompesch M, Skee D, Vande Bosch A, Murphy J, Ways K, Schwartz S: Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. *Diabetes Obes Metab* 2012;14:539–545.
- 15 Polidori D, Sha S, Ghosh A, Plum-Morschel L, Heise T, Rothenberg P: Validation of a novel method for determining the renal threshold for glucose excretion in untreated and canagliflozin-treated subjects with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2013;98:E867–E871.
- 16 Sha S, Devineni D, Ghosh A, Polidori D, Chien S, Wexler D, Shalayda K, Demarest K, Rothenberg P: Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. *Diabetes Obes Metab* 2011;13:669–672.
- 17 Levey AS, de Jong PE, Coresh J, El NM, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU: The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011;80:17–28.
- 18 Stenlof K, Cefalu WT, Kim KA, Jodar E, Alba M, Edwards R, Tong C, Canovatchel W, Meininger G: Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. *Curr Med Res Opin* 2014;30:163–175.
- 19 Neal B, Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Stein P, Desai M, Shaw W, Jiang J, Vercruysse F, Meininger G, Matthews D: Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS) – a randomized placebo-controlled trial. *Am Heart J* 2013;166:217–223.
- 20 Invokana® 100 mg film-coated tablets. Summary of product characteristics (2.12.2013–2.4.2014). High Wycombe, Janssen-Cilag, 2014.
- 21 Oliva RV, Bakris GL: Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. *J Am Soc Hypertens* 2014;8:330–339.
- 22 Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, Fagan NM, Woerle HJ, Johansen OE, Broedl UC, von EM: Renal hemodynamic effect of sodium-glucose co-transporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;129:587–597.
- 23 Thomson SC, Rieg T, Miracle C, Mansoury H, Whaley J, Vallon V, Singh P: Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. *Am J Physiol Regul Integr Comp Physiol* 2012;302:R75–R83.
- 24 Nicolle LE, Capuano G, Fung A, Usiskin K: Urinary tract infection in randomized phase III studies of canagliflozin, a sodium glucose co-transporter 2 inhibitor. *Postgrad Med* 2014;126:7–17.
- 25 Flynn C, Bakris GL: Noninsulin glucose-lowering agents for the treatment of patients on dialysis. *Nat Rev Nephrol* 2013;9:147–153.
- 26 CREDENCE Trial: 2014. <http://www.clinicaltrials.gov/ct2/show/NCT02065791?term=CREDENCE&rank=1>.